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Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation

An Observational Cohort Study

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Background and Purpose—We sought to determine the risk of stroke/thromboembolism and bleeding associated with reduced renal function in patients with atrial fibrillation and the risk of stroke and bleeding associated with warfarin treatment in specific estimated glomerular filtration rate (eGFR) groups.

Methods—We conducted a register-based cohort study and included patients discharged with nonvalvular atrial fibrillation from 1997 to 2011 with available eGFR.

Results—A total of 17 349 patients were identified with eGFR available at baseline. All levels of lower eGFR were associated with higher risk of stroke/thromboembolism and bleeding. Use of warfarin was associated with higher bleeding risk in all eGFR groups; hazard ratios 1.23 (95% confidence interval [CI], 0.97–1.56), 1.26 (95% CI, 1.14–1.40), 1.18 (95% CI, 1.07–1.31), 1.11 (95% CI, 0.87–1.42), 2.01 (95% CI, 1.14–3.54) in patients with eGFR ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min per 1.73 m^2, respectively. Use of warfarin was associated with lower risk of stroke/thromboembolism in patients with eGFR ≥15 mL/min per 1.73 m^2; hazard ratios 0.57 (95% CI, 0.43–0.76), 0.57 (95% CI, 0.51–0.64), 0.48 (95% CI, 0.44–0.54), 0.60 (95% CI, 0.45–0.80) in patients with eGFR ≥90, 60 to 89, 30 to 59, and 15 to 29 mL/min per 1.73 m^2, respectively. Use of warfarin was not associated with lower risk of stroke/thromboembolism in patients with eGFR<15 mL/min per 1.73 m^2; hazard ratio 1.18 (95% CI, 0.58–2.40).

Conclusions—In patients with atrial fibrillation, the risk of stroke and bleeding was associated with levels of renal function. Warfarin treatment was associated with higher risk of bleeding in all eGFR groups and lower risk of stroke in patients with eGFR≥15 mL/min per 1.73 m^2. **(*Stroke*. 2016;47:2707-2713. DOI: 10.1161/STROKEAHA.116.014422.)**

Key Words: atrial fibrillation ■ glomerular filtration rate ■ renal insufficiency, chronic ■ stroke ■ thromboembolism

Patients with reduced estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 have been excluded from randomized controlled trials of non–vitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation (AF),[1,2] and the efficacy of warfarin specifically in patients with AF and reduced eGFR has never been established from randomized controlled trials. Furthermore, observational studies have led to doubts about the use of warfarin in this population.[3,4]

Only few observational studies have reported eGFR in AF cohorts, and these have generally focused on either the risk of stroke associated with reduced renal function without anticoagulation[5] or the risk of bleeding associated with reduced renal function while on anticoagulation.[3] Data on the risks associated with mildly reduced renal function are sparse. We have previously studied the risk associated with coexisting chronic kidney disease and AF and the risks and benefits of anticoagulation in these patients,[6,7] but detailed levels of renal function based on creatinine measurements have not previously been available.

The aim of the current study was to examine the risk of stroke/thromboembolism and major bleeding associated with reduced eGFR in a large Danish AF cohort and to evaluate the risk of stroke and bleeding associated with warfarin anticoagulation

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according to the level of renal function categorized according to eGFR. We tested the hypotheses that the risk of stroke and bleeding could be related to the level of renal function in patients with AF and that warfarin would be associated with higher risk of bleeding and lower risk of stroke independent of renal function.

Methods

Study Setting

In Denmark, every resident is provided with a unique and permanent civil registration number that allows linkage of data from several nationwide registries on an individual level. In the Danish National Patient Registry, all patients discharged from a Danish hospital are coded according to the *International Classification of Disease* system.[8] All invasive therapeutic procedures are coded according to the Nordic Medical Statistics Committees Classification of Surgical Procedures. All prescriptions dispensed from Danish pharmacies are registered in the Danish Registry of Medicinal Product Statistics according to the Therapeutical Chemical system.[9] The Danish Civil Registration System keeps information on vital status and cause of death for every citizen.[10] The Danish Registry on Regular Dialysis and Transplantation holds complete and valid information on all Danish citizens treated with chronic renal replacement therapy.[11]

Study Population

We included all Danish residents discharged from a Danish hospital between 1997 and 2011 with a first-time primary diagnosis of AF or atrial flutter. Because information on medication relied on prescription claims and pharmacotherapy could have been changed or intensified in relation to index AF hospitalization, we began follow-up 7 days after discharge. We excluded patients who experienced major bleeding, stroke/thromboembolism, or death within the 7-day period, patients >100 or <30 years, patients with valvular AF, patients who received dabigatran, and patients who received chronic renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplant). Patients were followed up until December 31, 2011, emigration, death, initiation of chronic renal replacement therapy, or event. All *International Classification of Disease* codes used to define the study population, comorbidities, and outcomes are shown in Table I in the online-only Data Supplement.

Estimating Renal Function

We identified all serum creatinine measurements available between 1996 and 2011 from hospital laboratories in 3 different counties of Denmark. Serum creatinine measurements from the General Practitioner Laboratory of Copenhagen were also included. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formulae.[12] Baseline eGFR was estimated using the latest serum creatinine measurement up to 12 months before index AF hospitalization. For purposes of sensitivity, a mean eGFR was calculated for each patient based on all available serum creatinine measurements recorded within 12 months before index AF hospitalization. We categorized renal function as follows: eGFR ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min per 1.73 m^2. Renal function was determined time dependently throughout follow-up, ie, patients could switch eGFR group according to latest eGFR every time a new serum creatinine measurement was made.

Pharmacotherapy and Comorbidities

Baseline pharmacotherapy was defined using redeemed prescriptions from 180 days before discharge to 7 days hereafter. Use of warfarin was estimated time dependently throughout follow-up, as previously done,[7] by dividing the number of redeemed tablets with an estimated daily dose. Comorbidities for our population were determined as done in previous studies.[6,7]

Study Outcomes

Outcomes under investigation were as follows: (1) death/hospitalization from stroke/thromboembolism and (2) death/hospitalization from major bleeding. Stroke/thromboembolism was defined using diagnosis codes for ischemic stroke, transient ischemic attack, or systemic thromboembolism. Major bleeding was defined using diagnosis codes denoting severe gastrointestinal, intracranial, urinary tract, and airway bleeding.

Statistics

Incidence rates of stroke/thromboembolism and major bleeding according to renal function and warfarin treatment were estimated time dependently. The Aalen–Johansen method was used to determine the cumulative incidence of stroke/thromboembolism and major bleeding, accounting for competing risk of death. As sensitivity, this was also done using (1) only creatinine measurements from general practitioners

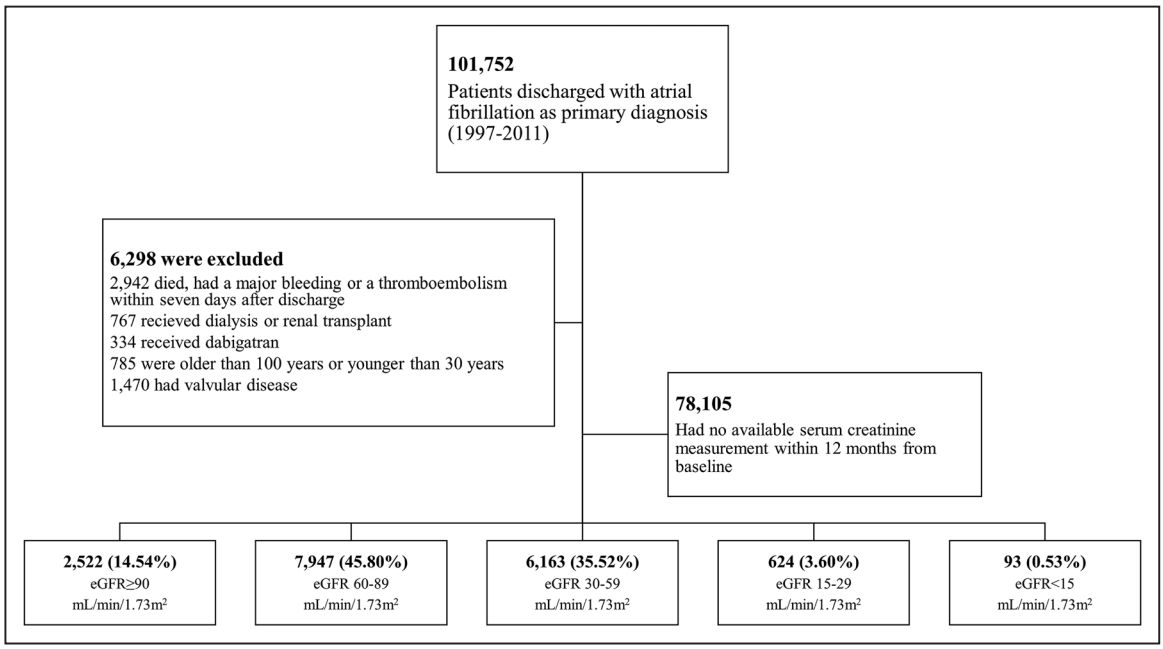

Figure 1. Flowchart of the population selection. eGFR indicates estimated glomerular filtration rate.

Table 1. Characteristics at Baseline in Relation to Renal Status

	eGFR≥90	eGFR 60–89	eGFR 30–59	eGFR 15–30	eGFR<15
No. of patients	2522	7947	6163	624	93
Age, median (IQR), y	61 (52–69)	70 (62–78)	80 (73–85)	83 (77–88)	78 (69–87)
Last measurement					
eGFR, median (IQR)	100 (94–111)	73 (66 -81)	49 (42–55)	25.(21–28)	12 (9–14)
Measurements from the last year					
eGFR, median (IQR)	98 (91–109)	73 (66–80)	51 (43–57)	27 (23–31)	14 (12–18)
No. of measurements, median (IQR)	2 (1–5)	3 (1–5)	3 (2–7)	7 (3–13)	11 (5–18)
Stroke comorbidity					
CHA_2DS_2-VASc, mean (SD)	1.53 (1.41)	2.44 (1.60)	3.59 (1.47)	4.32 (1.49)	3.81 (1.69)
Heart failure	135 (5.4)	842 (10.6)	1380 (22.4)	266 (42.6)	35 (37.6)
Hypertension	870 (34.5)	3518 (44.3)	3420 (55.5)	392 (62.8)	56 (60.2)
Age ≥75 y	292 (11.6)	2892 (36.4)	4346 (70.5)	518 (83.0)	54 (58.1)
Diabetes mellitus	226 (9.0)	593 (7.5)	571 (9.3)	106 (17.0)	20 (21.5)
Previous stroke	199 (7.9)	829 (10.4)	967 (15.7)	132 (21.2)	19 (20.4)
Vascular disease	250 (9.9)	1010 (12.7)	1258 (20.4)	208 (33.3)	30 (32.3)
Age 65–74 y	661 (26.2)	2477 (31.2)	1340 (21.7)	83 (13.3)	26 (28.0)
Women	738 (29.3)	3524 (44.3)	3545 (57.5)	339 (54.3)	41 (44.1)
Bleeding comorbidity					
HAS-BLED, mean (SD)	1.16 (1.05)	1.50 (0.97)	1.93 (0.86)	2.23 (0.89)	2.06 (0.91)
Age >65 y	953 (37.8)	5369 (67.6)	5686 (92.3)	601 (96.3)	80 (86.0)
Alcohol	215 (8.5)	280 (3.5)	128 (2.1)	14 (2.2)	5 (5.4)
Liver disease	81 (3.2)	112 (1.4)	74 (1.2)	11 (1.8)	<3
Previous bleeding	159 (6.3)	429 (5.4)	477 (7.7)	81 (13.0)	15 (16.1)
Hypertension	870 (34.5)	3518 (44.3)	3420 (55.5)	392 (62.8)	56 (60.2)
Previous stroke	199 (7.9)	829 (10.4)	967 (15.7)	132 (21.2)	19 (20.4)
Medication at baseline					
Warfarin	818 (32.4)	3620 (45.6)	2730 (44.3)	219 (35.1)	20 (21.5)
ADP receptor antagonist	61 (2.4)	230 (2.9)	207 (3.4)	26 (4.2)	6 (6.5)
NSAID	500 (19.8)	1589 (20.0)	1317 (21.4)	176 (28.2)	17 (18.3)
Aspirin	724 (28.7)	4916 (61.9)	3138 (50.9)	270 (43.3)	46 (49.5)
β-blocker	1340 (53.1)	4547 (57.2)	3411 (55.3)	347 (55.6)	57 (61.3)
Calcium channel blocker	545 (21.6)	2110 (26.6)	1891 (30.7)	205 (32.9)	33 (35.5)
RASi	662 (26.2)	2659 (33.5)	2632 (42.7)	328 (52.6)	39 (41.9)
Loop diuretics	379 (15.0)	2003 (25.2)	2837 (46.0)	480 (76.9)	69 (74.2)

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age 75 years (double weight), diabetes mellitus, stroke/thromboembolism (double weight), vascular disease, age 65–74, female sex; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m^2); HAS-BLED, hypertension, abnormal renal/liver function, previous stroke/thromboembolism, previous bleeding, labile international normalized ratio, elderly (age>75 years), alcohol abuse; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs; and RASi, renin–angiotensin system inhibitors.

and (2) only creatinine tests from index AF hospitalization. The risk of stroke/thromboembolism and major bleeding associated with renal function for warfarin-anticoagulated and nonanticoagulated patients, respectively, was examined using time-dependent Cox proportional hazards models. Patients with eGFR≥90 mL/min per 1.73 m^2 were used as reference. The risk of stroke/thromboembolism and major bleeding associated with warfarin treatment for patients with eGFR ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min per 1.73 m^2 was examined using time-dependent Cox proportional hazards models. Patients who did not receive warfarin were used as reference. A 2-sided $P<0.05$ was considered statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC) and R version 2.15.2 (R Development Core Team).

Ethics

Ethical approval is not required for retrospective registry-based studies in Denmark. The study was approved by the Danish Data Protection Agency (ref. no: 2007-58-0015/GEH-2014-012 I-Suite no: 02720).

Results

Characteristics of the Study Population

The selection of the study population is illustrated in Figure 1. We identified 101 752 patients with AF during the 15-year study period, and we excluded 6298 patients. Serum creatinine was available at baseline in 17 349 of the remaining patients. Median age at baseline was 73 (interquartile range [IQR], 64–81) years, and 9162 (52.8%) were women. Table 1 shows characteristics at baseline in relation to renal function.

Mean eGFR values calculated using all serum creatinine measurements from the last year before inclusion were comparable to the latest single eGFR measured before inclusion. Patients with eGFR 15 to 29 mL/min per 1.73 m^2 were oldest and had the highest CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years [double weight], diabetes mellitus, stroke/thromboembolism [double weight], vascular disease, age 65–74, female sex) and HAS-BLED scores (hypertension, abnormal renal/liver function, previous stroke/thromboembolism, previous bleeding, labile international normalized ratio, elderly [age>75 years], alcohol abuse). Patients with eGFR 60 to 89 mL/min per 1.73 m^2 were most likely to receive warfarin treatment, and patients with eGFR <15 mL/min per 1.73 m^2 were least likely to receive warfarin treatment. Of the 2520 patients in our study with CHA_2DS_2-VASc score 0 for men or 1 for women, 1541 (61.2%) had an eGFR <90 mL/min per 1.73 m^2 at baseline and 719 (28.5%) were in treatment with warfarin. Of the 93 patients with eGFR<15 mL/min per 1.73 m^2 at baseline, 17 (18.3%) initiated chronic renal replacement therapy during follow-up.

Follow-Up

Median follow-up was 4.0 (IQR, 1.4–7.8), 4.9 (IQR, 2.0–8.1), 3.5 (IQR 1.3–6.7), 1.3 (IQR, 0.3–3.5), and 0.5 (IQR, 0.1–1.4) years in patients with eGFR ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min per 1.73 m^2 at baseline, respectively.

Incidence of Stroke/Thromboembolism and Major Bleeding

Figure 2 shows 1-year cumulative incidence of stroke/thromboembolism and major bleeding according to renal function determined at baseline. Lower eGFR was associated with greater cumulative incidence of both stroke/thromboembolism and major bleeding.

Table 2 shows incidence rates of stroke/thromboembolism and major bleeding according to warfarin treatment and renal function. In patients with eGFR≥15 mL/min per 1.73 m^2 rates of stroke/thromboembolism were lower among patients who received warfarin than among patients who did not receive warfarin, and rates of major bleeding were higher among patients who received warfarin than among patients who did not receive warfarin. Patients with eGFR<15 mL/min per 1.73 m^2 had comparable rates of stroke/thromboembolism on and off warfarin and higher rates of bleeding on warfarin than off warfarin.

Table 3 shows results from the multivariable adjusted Cox proportional hazard models on stroke/thromboembolism and major bleeding. A stepwise decrease in eGFR level was associated with an incremental increase in risk of stroke/thromboembolism and major bleeding when using eGFR≥90 mL/min per 1.73 m^2 as a reference.

Figure 3 illustrates results from Cox proportional hazard models on stroke/thromboembolism and major bleeding associated with use of warfarin. In patients with eGFR≥15 mL/min per 1.73 m^2, warfarin was associated with lower risk of stroke. Warfarin was associated with higher bleeding risk across eGFR groups although insignificantly in patients with eGFR≥90 mL/min per 1.73 m^2 (hazard ratio, 1.23; 95% confidence interval, 0.97–1.56) and in patients with eGFR 15 to 29 mL/min per 1.73 m^2 (hazard ratio, 1.11; 95% confidence interval, 0.87–1.42). In patients with eGFR<15 mL/min per 1.73 m^2 not receiving dialysis, warfarin was not associated with lower risk of stroke (hazard ratio, 1.18; 95% confidence interval, 0.58–1.40), but was associated with higher risk of bleeding (hazard ratio, 2.01; 95% confidence interval, 1.14–3.54).

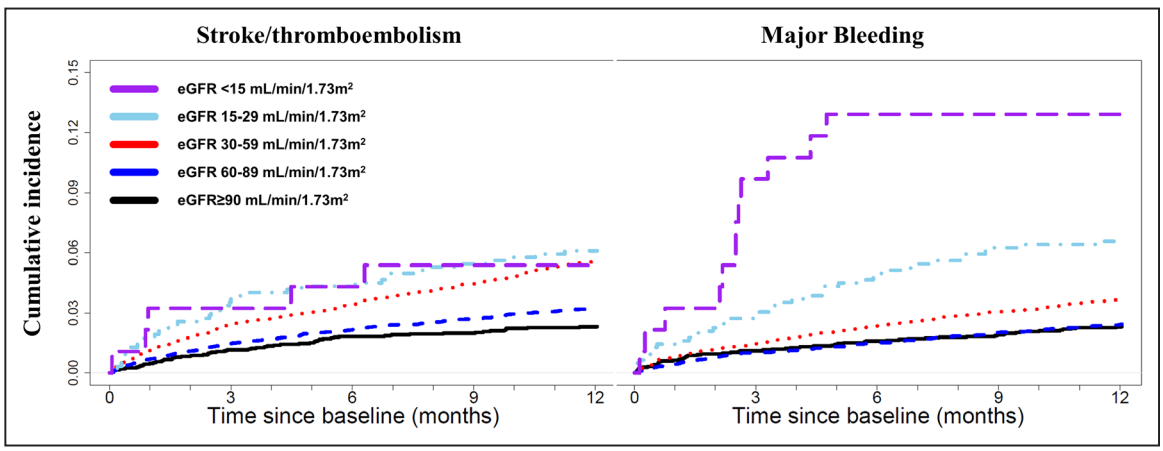

Figure 2. Cumulative incidence of stroke/thromboembolism and major bleeding according to eGFR. Renal function was determined with the last measurement available at baseline. The model is taking the risk of death from other causes (competing risks) into account. eGFR indicates estimated glomerular filtration rate.

Table 2. Incidence Rates of Stroke/Thromboembolism and Major Bleeding per 100 Person-Years According to eGFR and Warfarin Treatment

	Rates (95% CI; No. of Events)	
	Received Warfarin	Did Not Receive Warfarin
15-y follow-up		
Stroke/thromboembolism		
eGFR≥90	1.54 (1.22–1.86; 88)	1.65 (1.43–1.86; 228)
eGFR 60–89	1.73 (1.58–1.89; 455)	2.80 (2.64–2.96; 1120)
eGFR 30–59	2.34 (2.13–2.55; 482)	5.30 (5.03–5.57; 1508)
eGFR 15–29	4.36 (3.21–5.50; 56)	7.59 (6.51–8.67; 189)
eGFR<15	14.47 (5.50–23.45; 10)	13.61 (8.17–19.06; 24)
Major bleeding		
eGFR≥90	2.55 (2.14–2.96; 149)	1.44 (1.24–1.64;198)
eGFR 60–89	2.25 (2.07–2.43; 608)	1.74 (1.61–1.87; 700)
eGFR 30–59	3.15 (2.91–3.39; 676)	2.96 (2.76–3.16; 862)
eGFR 15–29	6.98 (5.53–8.43; 89)	6.40 (5.41–7.39; 161)
eGFR<15	21.74 (11.09–32.40; 16)	12.70 (7.39–18.00; 22)
1-y follow-up		
Stroke/thromboembolism		
eGFR≥90	2.52 (1.55–3.48; 26)	2.71 (2.06–3.36; 67)
eGFR 60–89	2.75 (2.25–3.25; 116)	4.09 (3.61–4.57; 279)
eGFR 30–59	4.06 (3.34–4.79; 121)	8.54 (7.73–9.36; 423)
eGFR 15–29	9.77 (5.38–14.16; 19)	13.57 (10.08–17.07; 58)
eGFR<15	14.14 (0–33.74; 2)	14.51 (2.90–26.12; 6)
Major bleeding		
eGFR≥90	3.18 (2.09–4.26; 33)	1.94 (1.39–2.49; 48)
eGFR 60–89	2.94 (2.43–3.46; 125)	2.88 (2.47–3.28; 196)
eGFR 30–59	3.39 (2.73–4.05; 102)	4.30 (3.73–4.88; 215)
eGFR 15–29	10.82 (6.19–15.44; 21)	8.98 (6.16–11.80; 39)
eGFR<15	36.01 (4.45–67.57; 5)	25.51 (9.70–41.32; 10)

eGFR and warfarin treatment were estimated time dependently throughout follow-up. CI indicates confidence interval; and eGFR, estimated glomerular filtration rate (mL/min per 1.73 m^2).

Sensitivity Analyses

Figures I and II in the online-only Data Supplement show cumulative incidence of stroke/thromboembolism and major bleeding by renal function determined with serum creatinine measurements obtained during index AF hospitalization. Figures III and IV in the online-only Data Supplement show cumulative incidence of stroke/thromboembolism and major bleeding by renal function as determined by using only serum creatinine measurements from general practitioners. In all analyses, Figures I through IV in the online-only Data Supplement, cumulative incidence of both stroke/thromboembolism and major bleeding were inversely correlated with eGFR. Figure V in the online-only Data Supplement shows median eGFR during the last 14 years before stroke/thromboembolism. For patients who experienced a stroke/thromboembolism, median eGFR decreased gradually during the study period, and our results were not driven by an immediate fall in eGFR before event.

Discussion

In this Danish cohort study including 17 349 AF patients with different levels of renal function, we found a stepwise higher risk of stroke/thromboembolism and major bleeding associated with decreasing levels of eGFR. Notably, the risk was higher in all patients with eGFR levels below 90 mL/min per 1.73 m^2. Furthermore, warfarin treatment was associated with lower risk

Table 3. Adjusted Hazard Ratio for Stroke/Thromboembolism and Major Bleeding According to eGFR and Warfarin Treatment

	Hazard Ratio (95% Confidence Interval)	
	Received Warfarin	Did Not Receive Warfarin
15-y follow-up		
Stroke/thromboembolism*		
eGFR≥90	1.00 (reference)	1.00 (reference)
eGFR 60–89	1.90 (1.58–2.29)	1.23 (1.11 - 1.36)
eGFR 30–59	1.86 (1.54–2.26)	1.50 (1.35 - 1.65)
eGFR 15–29	3.21 (2.38–4.32)	1.94 (1.65–2.28)
eGFR<15	11.55 (6.55–20.37)	4.11 (2.86–5.91)
Major bleeding†		
eGFR≥90	1.00 (reference)	1.00 (reference)
eGFR 60–89	1.96 (1.67–2.31)	1.71 (1.35–2.16)
eGFR 30–59	2.15 (1.82–2.54)	2.14 (1.69–2.72)
eGFR 15–29	4.66 (3.65–5.94)	3.68 (2.54–5.34)
eGFR<15	16.73 (10.79–25.96)	11.02 (6.04–20.10)
1-y follow-up		
Stroke/thromboembolism*		
eGFR≥90	1.00 (reference)	1.00 (reference)
eGFR 60–89	1.64 (1.22–2.22)	1.09 (0.91–1.30)
eGFR 30–59	2.07 (1.51–2.83)	1.53 (1.29–1.80)
eGFR 15–29	4.34 (2.62–7.20)	2.13 (1.60–2.83)
eGFR<15	10.01 (3.15–31.82)	3.09 (1.52–6.26)
Major bleeding†		
eGFR≥90	1.00 (reference)	1.00 (reference)
eGFR 60–89	1.87 (1.38–2.52)	1.26 (1.11–1.43)
eGFR 30–59	1.77 (1.28–2.45)	1.48 (1.30–1.68)
eGFR 15–29	4.54 (2.82–7.31)	3.11 (2.59–3.75)
eGFR<15	30.60 (15.78–59.31)	8.79 (6.20–12.46)

eGFR indicates estimated glomerular filtration rate (mL/min per 1.73 m^2).

*Model adjusted for congestive heart failure, hypertension, diabetes mellitus, previous stroke/thromboembolism, sex, age, vascular disease, and use of aspirin and ADP receptor antagonists. eGFR and warfarin treatment were estimated time dependently throughout follow-up.

†Model adjusted for hypertension, age, previous stroke, previous bleeding, liver disease, alcohol abuse, age, and use of aspirin and ADP receptor antagonists. eGFR and warfarin treatment were estimated time dependently throughout follow-up.

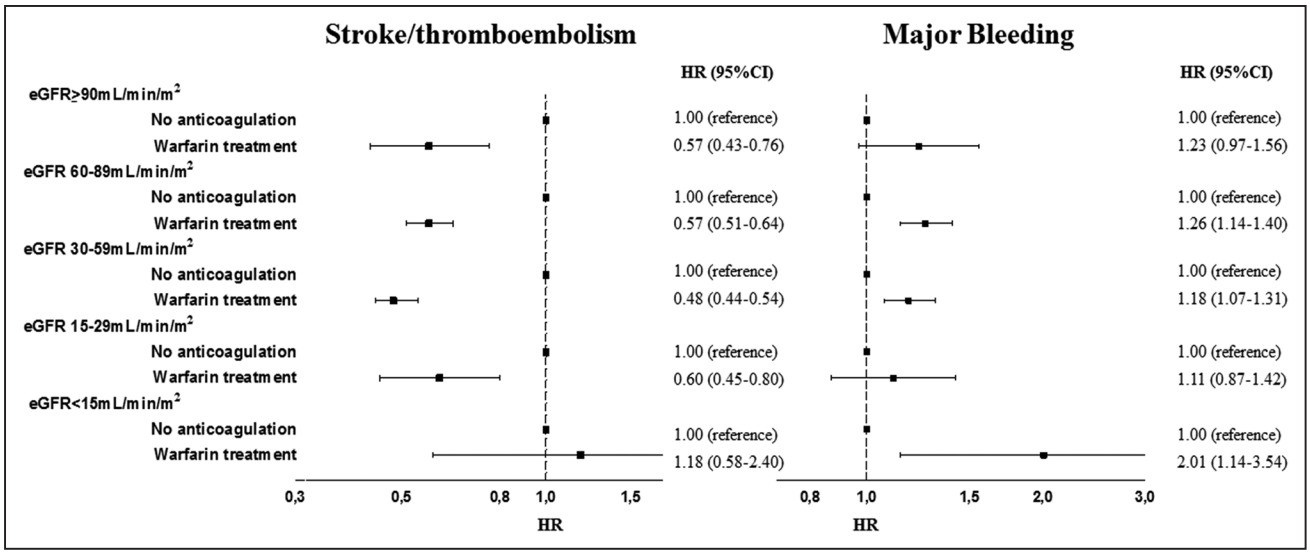

Figure 3. Adjusted hazard ratio (HR) for stroke/thromboembolism and major bleeding according to estimated glomerular filtration rate (eGFR) and warfarin treatment. The model with stroke/thromboembolism as outcome was adjusted for congestive heart failure, hypertension, diabetes mellitus, previous stroke/thromboembolism, sex, age, vascular disease, and use of aspirin and ADP receptor antagonists. Warfarin treatment and eGFR were estimated time dependently throughout follow-up. The model with major bleeding as outcome was adjusted for hypertension, age, previous stroke, previous bleeding, liver disease, alcohol abuse, age, and use of aspirin and ADP receptor antagonists. Warfarin treatment and eGFR were estimated time dependently throughout follow-up. CI indicates confidence interval.

of stroke in all patients with eGFR>15 mL/min per 1.73 m^2, but not in patients with eGFR<15 mL/min per 1.73 m^2. Warfarin was generally associated with higher risk of bleeding across all eGFR groups after adjustment for relevant risk factors.

Risk of Stroke and Bleeding Associated With Reduced eGFR

Kidney dysfunction is associated with an increase in inflammatory and procoagulant biomarkers, including C-reactive protein, fibrinogen, factor VII, and factor VIII[13,14] and has been considered a marker of organ damage caused by hypertension or diabetes mellitus.[2] Notably, kidney dysfunction as an independent risk factor for stroke in AF has been garnering attention, and the addition of kidney dysfunction to various stroke risk stratification tools in AF has previously been studied.[15,16] On the contrary, kidney dysfunction is associated with hemostatic dysfunction, including decreased levels of glycoprotein IIb and IIIa, decreased activity of von Willebrand Factor and altered arachidonic acid metabolism.[17,18] Results from other cohorts have raised safety concerns on the use of warfarin in patients with severely reduced renal function.[3] A recent cohort study by Jun et al[3] reported gradually higher crude rates of bleeding associated with reduced renal function in patients with AF who received warfarin; however, after adjustment for relevant risk factors, this association was only significant among patients with eGFR<15 mL/min per 1.73 m^2.

We found that all levels of eGFR<90 mL/min per 1.73 m^2 were associated with higher risk of stroke after adjustment for risk factors included in the CHA_2DS_2-VASc score. Of the 2520 patients in our study with CHA_2DS_2-VASc score 0 for men or 1 for women, 1541 (61.15%) had an eGFR<90 mL/min per 1.73 m^2 at baseline and 719 (28.53%) were in treatment with warfarin. Our study was not designed or powered to investigate the net clinical benefit of warfarin in these patients, but our results suggest that the CHA_2DS_2-VASc score would identify more patients with AF with increased risk of stroke if reduced renal function was included.

Risks and Benefits of Warfarin Treatment in Patients With Severely Reduced Renal Function

There are no published data from randomized trials of oral anticoagulation specifically in AF patients with eGFR<30 mL/min per 1.73 m^2, and we are aware of only a single previous observational study with available creatinine measurements that has studied the safety and efficacy of warfarin in these patients.[19] Carrero et al[19] found a lower risk of stroke/thromboembolism with warfarin in post–myocardial infarction AF patients with eGFR<15 mL/min per 1.73 m^2. They also found lower bleeding rates on warfarin than on off warfarin, indicating possible selection bias, and the post–myocardial infarction nature of their study makes generalization to a broader AF population difficult. In the present study, warfarin treatment was associated with lower risk of stroke in all patients with eGFR>15 mL/min per 1.73 m^2, but not in patients with eGFR<15 mL/min per 1.73 m^2.

We have previously found warfarin to be associated with lower risk of stroke, and all-cause mortality in patients with diagnosed non–end-stage chronic kidney disease and in patients on chronic renal replacement therapy. Creatinine measurements have not previously been available for our cohort, but a previous sample of 110 diagnosed patients with non–end-stage chronic kidney disease indicated that the majority of these patients (75.5%) had an eGFR>15 mL/min per 1.73 m^2. Patients on chronic renal replacement therapy were excluded from the present study, and these patients were younger with less comorbidity than the patients with eGFR<15 mL/min per 1.73 m^2 analyzed in this study.

Clinical Implications

Our results highlight the importance of optimal renoprotective treatment to prevent stroke/thromboembolism and bleeding

in patients with AF and mild to moderate reduced renal function. Our results also suggest that nondialysis AF patients with eGFR<15 mL/min per 1.73 m^2 might not benefit from anticoagulation therapy with warfarin. Because of their renal excretion, non–vitamin K antagonist oral anticoagulants should not be used in patients with eGFR<15 mL/min per 1.73 m^2 and our results suggest that physicians should not abstain from starting a non–vitamin K antagonist oral anticoagulants over warfarin in anticipation of a declining renal function; if the eGFR falls <15 mL/min per 1.73 m^2, no anticoagulant should be used. At present, stroke prevention in this group of patients should focus on other factors than medical anticoagulation, ie, blood pressure control, smoking cessation, and a healthy diet. Future research should seek to develop new medical solutions for stroke prevention among patients with eGFR <15 mL/min per 1.73 m^2.

Limitations

The study is limited by the observational design, and the small number of patients with eGFR<15 mL/min per 1.73 m^2. We had no information on many clinical measures including international normalized ratio, body mass index, smoking status, blood pressure, hemoglobin levels, blood lipid levels, and proteinuria, and residual confounding from these or other factors cannot be excluded. Creatinine measurements were only available from 3 of 15 counties in Denmark. Thus, this reduced the number of patients available for inclusion. However, we had access to all serum creatinine measurements analyzed in the medical laboratories of these counties; hence, we have no reason to believe that this created substantial selection bias.

Conclusions

In a large Danish cohort of AF patients, risk of stroke/thromboembolism and major bleeding were significantly associated with the level of renal function. Warfarin treatment was associated with higher risk of bleeding in all eGFR groups and lower risk of stroke/thromboembolism in patients with eGFR >15 mL/min per 1.73 m^2.

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Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation: An Observational Cohort Study

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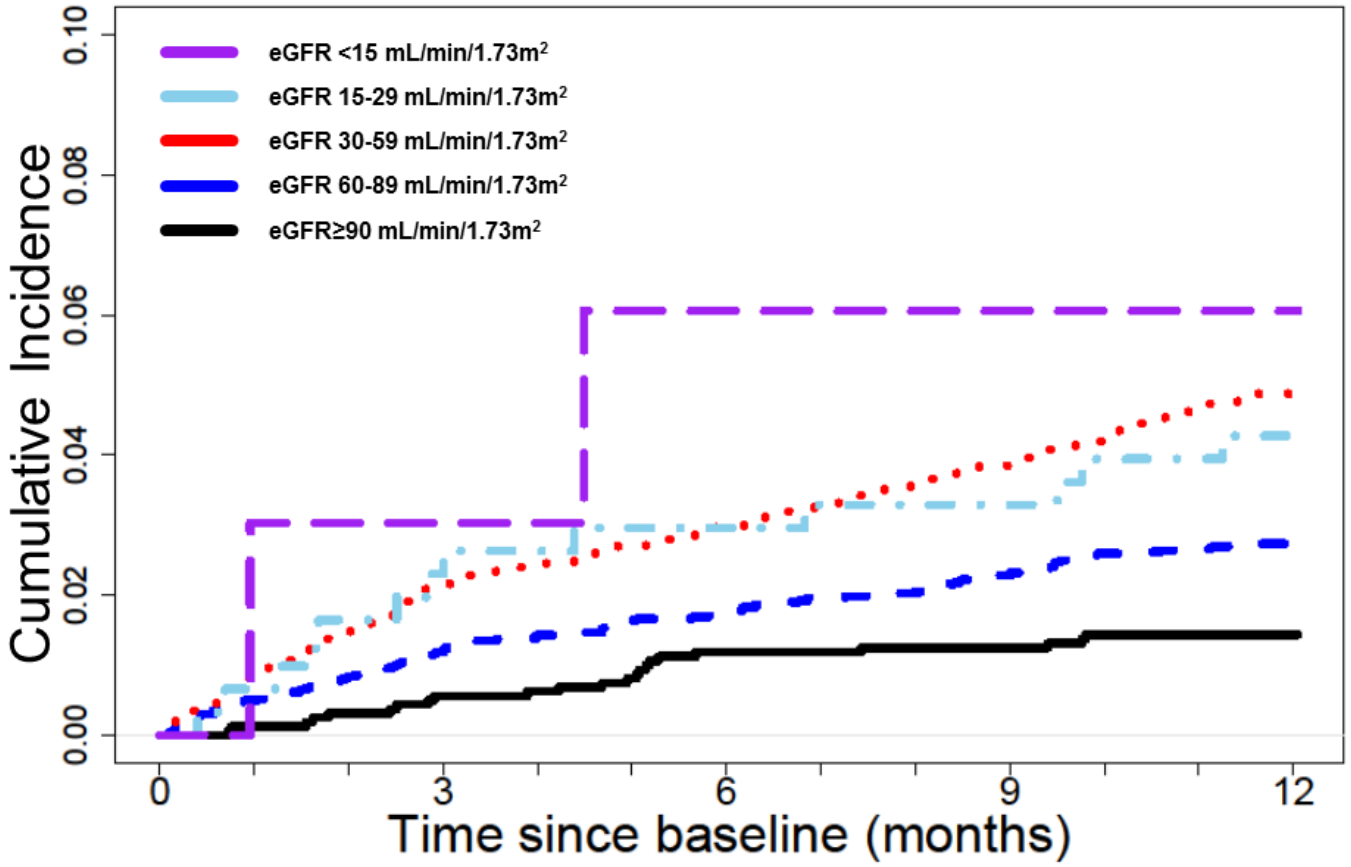
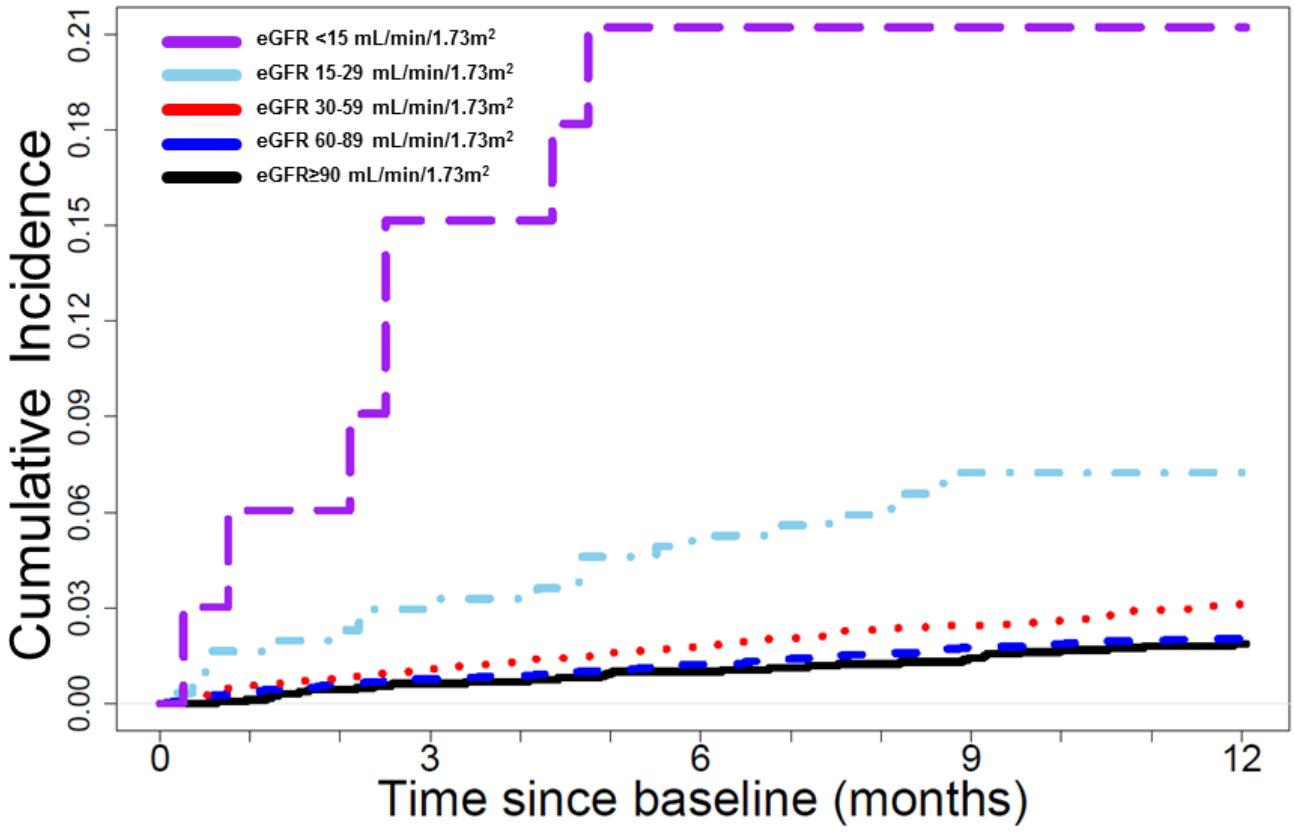
Online Supplement

Supplemental Figure I. Cumulative Incidence of Stroke/thromboembolism according to Renal Function



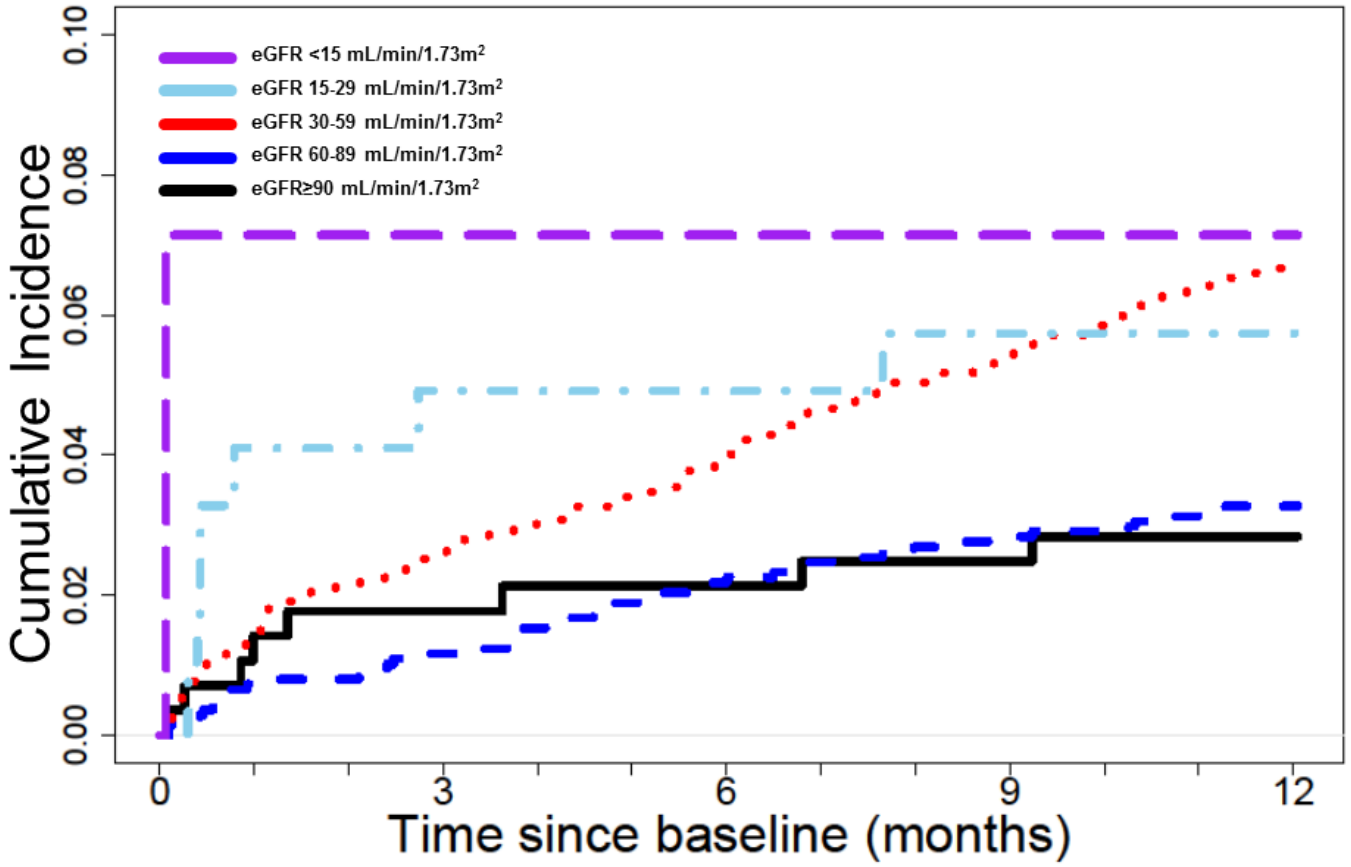
Caption: Cumulative Incidence of stroke/thromboembolism according to renal function. Renal function was determined at baseline. Only patients with creatinine measurements from index atrial fibrillation hospitalization were (n=10,486). The model is taking the risk of death from other causes (competing risks) into account.

Supplemental Figure II. Cumulative Incidence of Major bleeding according to Renal Function



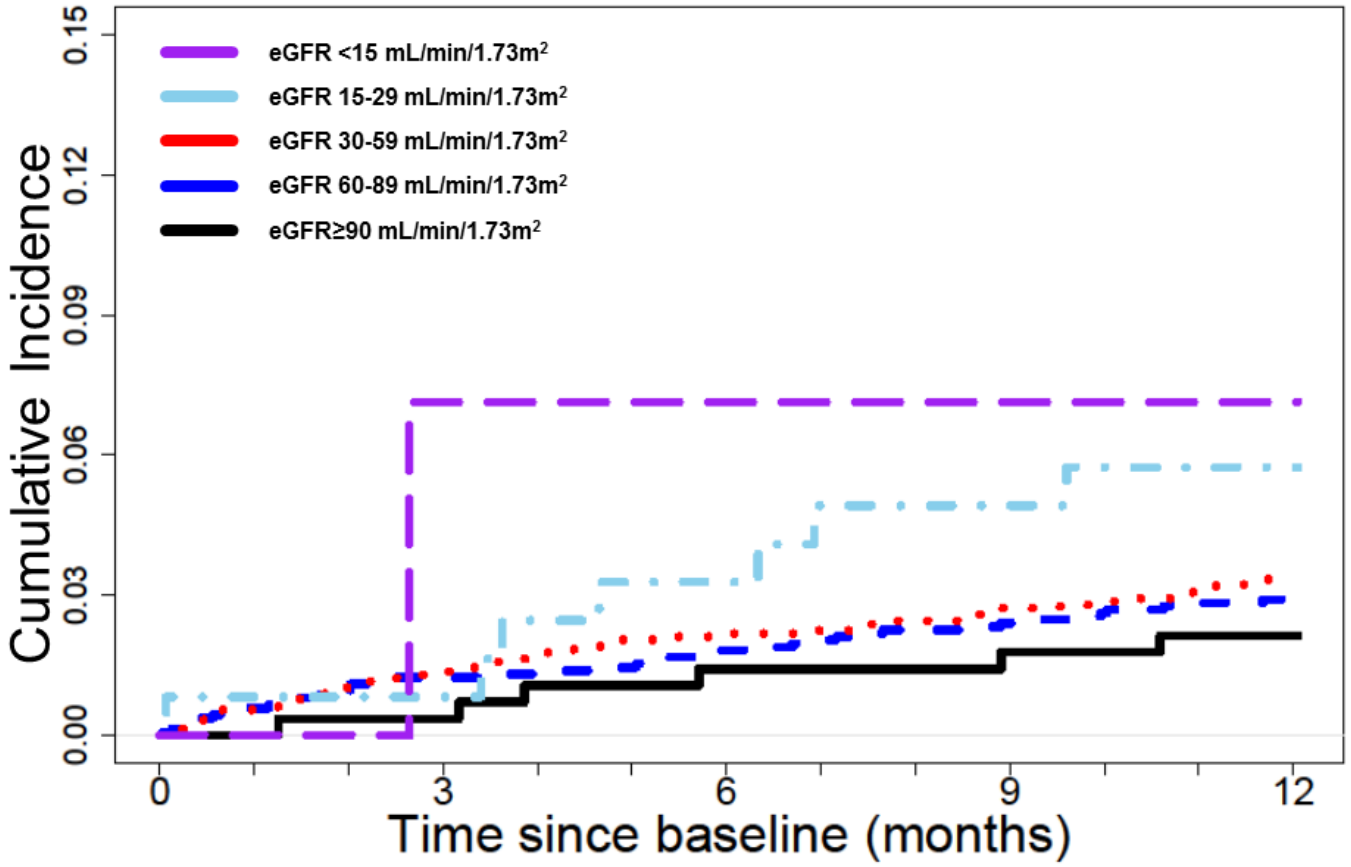
Caption: Cumulative Incidence of major bleeding according to renal function. Renal function was determined at baseline. Only patients with creatinine measurements from index atrial fibrillation hospitalization were included (n=10,486). The model is taking the risk of death from other causes (competing risks) into account.

Supplemental Figure III. Cumulative Incidence of Stroke/thromboembolism according to Renal Function



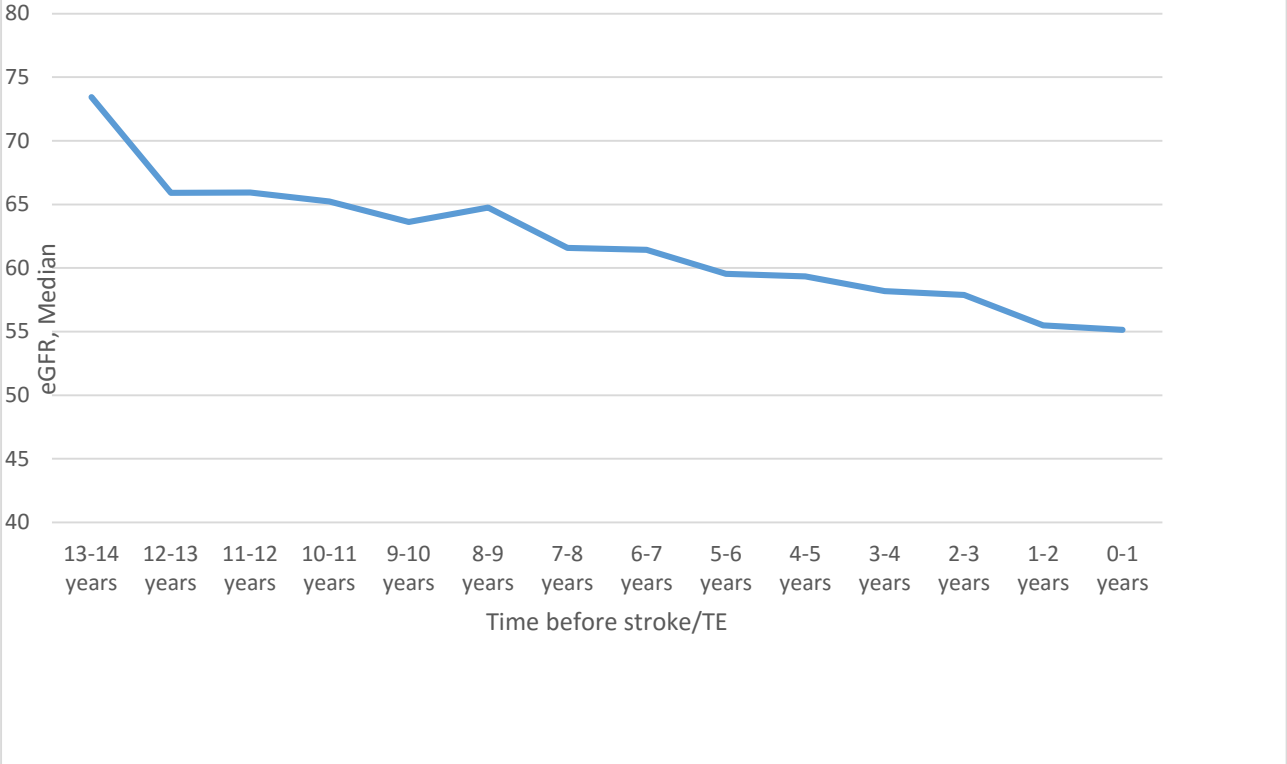
Caption: Cumulative Incidence of stroke/thromboembolism according to renal function. Renal function was determined at baseline. Only patients with creatinine measurements from general practitioners (n=3,262) were included. The model is taking the risk of death from other causes (competing risks) into account.

Supplemental Figure IV. Cumulative Incidence of Major Bleeding according to Renal Function



Caption: Cumulative Incidence of major bleeding according to renal function. Renal function was determined at baseline. Only patients with creatinine measurements from general practitioners (n=3,262) were included. The model is taking the risk of death from other causes (competing risks) into account.

Supplemental Figure V. Median eGFR before stroke



Time before stroke/TE	13-14 years	12-13 years	11-12 years	10-11 years	9-10 years	8-9 years	7-8 years	6-7 years	5-6 years	4-5 years	3-4 years	2-3 years	1-2 years	0-1 years
eGFR, median	73.42	65.92	65.94	65.24	63.62	64.74	61.58	61.42	59.53	59.35	58.18	57.88	55.5	55.14
n=	34	444	119	230	1012	458	631	1102	917	1071	1177	1339	1409	1759

Supplemental Table 1. Diagnoses, surgical procedures, and pharmacotherapy used for defining the population, comorbidity, and outcomes

Non-valvular atrial fibrillation

Presence of	*ICD10*:I48 *ICD8*: 4279
Absence of:	*ICD8*:39500, 39501, 39502, 39508, 39509, 39600, 3601, 39602, 39603, 39604, 39608, 39609. *ICD10*: Z952, Z954, I05, I06, I080A, I081A, I082A, I083A *NCSP:* KFKD, KFKH, KFMD, KFMH, KFMA20, KFMA32A, KFGE, KFJF

Comorbidity

Diabetes Mellitus	Defined from treatment	*Treatment:* Glucose-lowering medication
Heart Failure	Defined from diagnosis and treatment	*ICD8: 425, 4270-4271* *ICD10:* I110, I42, I50, J819. *Treatment:* Loop-diuretics.
Hypertension	Defined from combined treatment with at least two classes of antihypertensive drugs. This definition has a specificity of 94.7 % and a positive predictive value of 80.0%	*Treamtent:* Renin-angiotensin system inhibitors, calcium channel *blockers, vasodilators, non-loop-diuretics, adrenergic α-antagonists.*
Previous stroke/thromboembolism	Defined from diagnosis	*ICD8:* 433-438, 444 *ICD10:* G458-459, I63-I64, I74
Vascular disease	Defined from diagnosis	*ICD8:* 410, 440 *ICD10:* I21-I22, I700, I702-I709
Alcohol Abuse	Defined from diagnosis and reported adverse alcohol consumption during hospitalization	*ICD8:* 291, 303, N979-N980 *ICD10:* E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, *O354, T51, Z714, Z721.*
Drug consumption	Defined from treatment with non-steroidal anti-inflammatory drugs.	*Treatment:* NSAID's.

Liver Disease	Defined from diagnosis	*ICD8:* 070, 155, 571-573. *ICD10: B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944.*
Previous Bleeding	Defined from diagnosis	*ICD8:* 430-431, N852-N853 *ICD10:* I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066.

Outcomes

Stroke/thromboembolism	Death from or diagnosis of peripheral arterial embolism, stroke, and transient ischemic attack	*ICD10:* G458-G459, I63-I64, I74.
Major Bleeding	Death from or diagnosis of gastrointestinal, intracranial, urinary tract or airway bleeding	*ICD10:* I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066.

ICD8: 8th revision of the International Classification of Diseases system

ICD10: 10th revision of the International Classification of Diseases system

NCSP: The Nordic Medical Statistics Committees Classification of Surgical Procedures